

drawings, but what would be understood by persons skilled in the art. *In re Chilowsky*, 108 USPQ 321, 324 (CCPA 1956). Further, the enablement standard of 35 U.S.C. § 112 allows for experimentation. Indeed, even “a considerable amount of experimentation is permissible if it is merely routine.” *In re Wands*, 8 USPQ 2d 1400, 1404 (Fed. Cir. 1988).

The fact that the ‘501 application enabled the claimed invention was addressed at length in the amendment filed March 20, 1997 and was supported by the Declaration of Professor Young dated March 19, 1997.¹ Professor Young’s declaration was not merely conclusionary but was based on scientific reasoning and authorities. As such, it is entitled to considerable weight. See eg: *In re Alton*, 37 USPQ 2d 1578 (Fed. Cir. 1996).

The Office Action states that “the claims embrace every synthetic peptide which can be produced from the putative *env* ORF and which is reactive with antibodies present in sera from individuals infected with HIV.” The Office Action urges that “the actual number of peptide species is not *a priori* determinable.” In fact, there is no requirement that the actual number of species must be *a priori* determinable. The issue is whether the species could have been identified without “undue experimentation.” *In re Wands*, *supra*.

Applicants submit that the number of synthetic peptides required to cover the entire *env* ORF and the scale of the experiments needed to screen these synthetic peptides could have been routinely handled by one skilled in the art prior to October 31, 1984. More than ten references were cited in the previously submitted Dr. Young’s Declaration to demonstrate that prior to October 31, 1984 one skilled in the art was fully capable of synthesizing peptides from 15 to 40 amino acids (Young paragraph 7). The ‘501 application specifically teaches that HIV *env* ORF

¹References herein are to the Young Declaration of March 19, 1997 unless noted otherwise.

encompasses only 855 amino acids and sets forth the specific sequence thereof (page 9, lines 22-23, and Figure 4 in the '501 specification). If one skilled in the art made 10-mer peptides without any guidance as to which part of *env* region was more likely to be antigenic, one would only need to synthesize less than 90 peptides to cover the entire HIV *env* region. Alternatively, if one skilled in the art made 20-mer peptides with a 10 amino acid overlap, the number of synthetic peptides required would still be the same. This limited number of synthetic peptides could easily be screened for specific binding to HIV antibodies by ELISA analysis in one or two 96-well plates.

The Office Action questions whether the use of Hopp method was so widespread in 1984 that one skilled in the art would have been automatically led to its application to the sequence of *env* ORF taught in '501 specification. As a threshold matter, one skilled in the art could have made and used the present invention without relying on Hopp method. As above-discussed one could have synthesized less than 90 peptides and scanned the entire *env* ORF for antigenic epitopes.

Nevertheless, the Hopp method was published in two separate well-known and leading journals, *i.e.*, *PNAS* and *Mol. Immun.* These journals are routinely reviewed by general scientific audience. (See Young paragraph 4). Furthermore, the abstract of the 1983 Hopp reference clearly states:

A computerized method for predicting the locations of protein antigenic determinants is presented which requires only the amino acid sequence of a protein and no other information. This procedure has been used to predict the major antigenic determinant of the hepatitis B surface antigen, as well as antigenic sites on a series of test proteins of known antigenic structure [Hopp & Woods (1981) *Proc. Natl. Acad. Sci. U.S.A.* 78, 3824-3828.] The method is suitable for use in smaller personal computers and is written in the BASIC language in order to make it available to investigators with limited computer experience and/or

resources. A means of locating multiple antigenic sites on a homologous series of proteins is demonstrated using the influenza hemagglutinin as an example.

With such an inviting and user-friendly presentation, it is hard to imagine that any scientist would not be automatically led to the Hopp method. As proved later, “[i]n the years since then, the method has been used widely and has played a vital role in many antigenic studies.” (Hopp et al., “*Retrospective: 12 Years of Antigenic Determinant Predictions, and More,*” *Peptide Research*, 6(4): 183-190, 1993).

The Office Action admits that “immunoassays designed to measure the binding of native protein or synthetic peptide were developed” prior to the filing of the present invention. The Office Action states, however, that “for detecting serum antibodies directed toward retroviral protein the cited art is ambiguous”. The Office Action then implies that antibodies directed against native proteins or synthetic peptides behave differently in binding assays than antibodies directed against retroviral proteins. No basis has been offered to explain this statement or why such distinction is necessary. In the absence of any reason or explanation to support the Office Action’s assertion, Dr. Young’s Declaration is more than adequate to establish that the assays are equally applicable to antibodies directed against native or synthetic peptides as well as antibodies directed against retroviral proteins. (See Young paragraphs 8 and 15). In re Alton, supra.

The Office Action questions whether one skilled in the art could predict from the sequence which synthetic peptide would be antigenic. As above-established, one skilled in the art could have made and used the present invention without knowing in advance which synthetic peptide will be antigenic. Routine screening of less than 90 peptides is all that was required. Such routine experimentation is well within the realm of enablement standard set by the Court (*In re Wands*, 8 USPQ2d 1400, 1404, Fed. Cir. 1988). Also, as above-discussed, the Hopp

method would have allowed one skilled in the art to predict which peptide would be antigenic, even though such *a priori* prediction is not required for enablement.

The Office Action challenges Dr. Young's assertion that based on the teaching of '501 specification one would have understood that synthetic peptides would be useful in the immunoassays described in the '501 specification. In the DESCRIPTION OF THE SPECIFIC EMBODIMENTS, the specification states: "The polypeptides or immunologically active fragments thereof may find use as diagnostic reagents" (page 11, lines 5-9). At page 14, lines 17-26, an entire paragraph is devoted to immunoscreening assays for HIV antibody detection using expression products as well as "immunogenic fragments thereof having immunogenic sites" (page 14, line 18). In the SUMMARY OF THE INVENTION, the specification not only teaches recombinant expression of polypeptides but also teaches that "[b]ased on the nucleotide sequences, synthetic peptides may also be prepared" (page 3, line 15-16). There is no basis to exclude synthetic peptides from "immunologically active fragments" and "immunogenic fragments thereof having immunogenic sites" in view of the specification teaching at page 3.^{2/}

The Office Action also challenges Dr Young's conclusion that "those skilled in the art could have, without undue experimentation, used the sequence of ARV-2 env provided in the '501 application to generate synthetic peptides representing most of the HIV glycoprotein. These peptides could then have been tested using standard assays known in the art, and immunogenic regions of HIV Env identified." The Office Action urges that "the art Young relies on is directed toward antibody recognition not to immunogenicity". Applicants respectfully point out that the

^{2/}Much the same issue is raised in the office action when it asserts that the specification does not contain a written description of the invention as required by 35 U.S.C. § 112. That rejection is addressed below.

claims recite “an envelope (*env*) antigen” and the claim is directed to antibody recognition.

Therefore, the art cited in Dr. Young’s Declaration fully supports the claimed invention. The office action has not effectively rebutted Dr. Young’s declaration.

In summary, the ‘501 specification teaches the sequence of HIV *env* ORF and that synthetic of *env* antigen peptides can be used to detect HIV antibodies in human samples. Prior to the filing of the present invention, techniques and methods were available to allow one skilled in the art to routinely synthesize synthetic peptides and screen them for antibody binding. Therefore at the time that the parent application was filed, the invention was fully enabled by the teaching provided in the ‘501 specification and the knowledge available in the art. Withdrawal of the rejection is respectfully requested.

The office action also asserts at page 17 that the specification does not contain a written description of the claimed invention as required by 35 U.S.C. § 112. Such rejection is respectfully traversed. Indeed, the claimed invention is fully supported even in the earliest ‘501 parent application.

In determining whether a specification supports the claim, the specification as a whole must be considered. In re Chilowsky, supra. Here, as developed above, the specification, speaking to one skilled in the art, specifically discusses the use of immunologically active fragments “as diagnostic reagents” (page 11, line 6) or for “screening antisera from patients blood to determine whether antibodies are present which bind to hTLR antigens” (page 14, lines 17-21). The specification also specifically teaches that “a wide variety of assay techniques can be employed, involving label or unlabeled antigens” (page 14, lines 21-23) and, as the office action acknowledges, contains a working example of an immunoassay employing an *env* protein.

It appears that the heart of the rejection is the assertion that the “entire thrust of Applicant’s specification and examples is to recombinantly produce HIV peptides and fragments thereof,” and that it does not contain any description of the use of synthetic peptides in an immunoassay. That assertion ignores the clear thrust at page 3 of the ‘501 specification.

The office action concedes that the specification does teach the use of “HIV polypeptides and fragments thereof” in an env based immunoassay. The office action, however, unduly restricts the specific statement under the Summary of the Invention which teaches that the invention equally contemplates the use of synthetic peptides. The relevant portion of the Summary of the Invention reads:

“Summary of the Invention

Nucleotide sequences and expression of nucleotide sequences are provided for detecting the presence of complementary sequences associated with a retroviral etiologic agent for lymphadenopathy syndrome or acquired immune deficiency syndrome (AIDS), and for producing polypeptides.....Based on the nucleotide sequences, synthetic peptides may also be prepared.”

Nothing in that summary in any way limits the application of the last sentence. The last sentence does not say that synthetic peptides may only be used for vaccine; the statement does not limit the use of synthetic peptides as precursor proteins subject to further manipulation, or for any other purpose. On the contrary, the specification at page 3 clearly and unambiguously states that based on the nucleotide sequences, synthetic peptides may also be prepared. There is simply no basis to exclude any portion of the specification teachings with respect to the use of peptides

made from the nucleotide sequences. The specification does, indeed, provide a written description of the invention as required by 35 U.S.C. § 112.

The Rejection Under 35 U.S.C. §112, second paragraph

Claims 60-67 stand rejected as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The Office Action objects to the recitation “a synthetic polypeptide comprising an envelop antigen comprising an immunogenic amino acid sequence of the *env* domain of HIV, wherein said antigen is a synthetic polypeptide”.

In order to expedite prosecution the term “immunogenic” has been deleted from the claim. Withdrawal of the rejection is respectfully requested.

Priority Date Based Rejections

Claims 60-67 stand rejected under 35 U.S.C. §102(b) and 102(e) as being anticipated by Chang et al., (US Patent 4,774,175) and Cosand (US Patent 4,629,783). As established above, the present invention was fully enabled by the parent ‘501 application and has a priority date of October 31, 1984. All of the references cited above were filed later than the ‘501 application and thus do not qualify as prior art. Withdrawal of the rejections is respectfully requested.

The Rejection Under 35 U.S.C. §103

Claims 60-67 stand rejected as being unpatentable over either the combined teachings of Schupbach et al., Sarngadharan et al., and Popovic et al., or in combination with Levy (US 4,716,102) and in view of the level of skill in the art as set forth in the Young Declaration. This rejection is respectfully traversed.

The rejection completely ignores the true confusion in the art in 1984 at the time the '501 application was filed both with respect to the nature of the HIV virus and with respect to the possible envelope portion of any putative virus. The confusion in the art is apparent from the face of the very references cited by the office action as developed in the last amendment which discussed, inter alia, Schupbach, Samgadharan and Popovic. Levy, newly cited, is simply not adequate to lead to the claimed invention.

While Levy professed to have an ARV2 containing cell line, that is a far cry from having the sequence of the genomic sequence or the sequence of the envelope portion of the cell line. Given the confusion in the art, there is no basis to conclude that Popovic and Levy (or any of the other workers) had the same virus or even a closely related virus. The cited art does not provide any basis for the combination postulated by the office action.

Withdrawal of the rejection is respectfully requested.

In summary, the present invention was described and enabled by the '501 specification and is not *prima facie* obvious to one of ordinary skill in the art at the time of the invention was made. Withdrawal of the rejection and a speedy allowance of all pending claims are respectfully requested.

Respectfully submitted,

Date: November 26, 1997

By: Alisa A. Harbin

Alisa A. Harbin

Registration No. 33,895

by Alisa A. Harbin Date 11/26/97

Chiron Corporation
Intellectual Property Dept.-R440
4560 Horton Street
Emeryville, CA 94608-2916